

## Original Article

# Characteristics of Patients With Myocardial Infarction Occurring in the Early Morning Hours

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## ABSTRACT

**Background:** Circadian fluctuations in acute myocardial infarction (AMI) onset have been noted, peaking between 06:00 and 12:00 hours. While myocardial ischemia can occur anytime, circadian variation may influence acute ischemic heart disease onset. This study aimed to evaluate the impact of circadian rhythm on clinical and angiographic characteristics of ST-elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PPCI).

**Methods:** In this prospective study, we enrolled 433 consecutive patients diagnosed with acute STEMI who underwent PPCI. Patients were assigned to 2 groups based on the time of AMI onset: the first group included patients with morning onset of AMI (between 06:00 and 12:00 hours), and the second group included those with AMI onset at other times.

**Results:** Patients with morning presentation had higher initial and post-flow achievement thrombus scores, lower initial TIMI flow scores ( $P=0.035$ ,  $P=0.016$ , and  $P=0.004$ , respectively), and more frequent bailout glycoprotein IIb/IIIa use.

**Conclusions:** Patients experiencing STEMI symptom onset in the morning had a higher thrombus burden than those with symptom onset at other times. (*Iranian Heart Journal 2024; 25(3): 27-34*)

**KEYWORDS:** Early morning, STEMI, Circadian rhythm, Primary percutaneous coronary intervention, TIMI flow, Acute coronary syndrome

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Although mortality rates have decreased in recent years, coronary artery disease remains a leading cause of morbidity and mortality.<sup>1</sup> Even though myocardial ischemia can occur at any time of day, circadian variation has been confirmed for the onset of acute ischemic heart disease.<sup>2</sup> Pell and D'Alonzo<sup>3</sup> initially described the circadian pattern of acute

myocardial infarction (AMI) in 1963, with AMI showing the highest incidence in the morning, with a peak incidence between 06:00 and 12:00 hours.<sup>4</sup> The circadian rhythm of infarction appears to be altered by several factors.<sup>2</sup> Many physiological pathways could contribute to plaque rupture in the morning, including increased sympathetic tension, morning threshold for

platelet aggregation, and myocardial oxygen demand, along with decreased plasma fibrinolysis activity.<sup>3</sup> Patients with morning onset of AMI may have a different clinical outcome with a higher incidence of recurrent acute coronary syndrome (ACS) death and revascularization.<sup>4</sup> Knowing these pathophysiologic mechanisms of AMI will likely help to guide the treatment and lower its mortality and morbidity rates.<sup>3</sup> The current work aimed to evaluate the clinical and angiographic characteristics of patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) presenting in the morning hours.<sup>5</sup>

## METHODS

### Study Population

A total of 433 patients were prospectively enrolled in this study from December 2022 through November 2023 at the Cardiology Department. All patients were diagnosed with acute STEMI and underwent PPCI. The study adhered to international agreements (World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”) and received approval from the local ethics committee in December 2022 (approval reference 36217/12/22). Informed written consent was obtained from all participants. STEMI diagnosis was based on ST-segment elevation in at least 2 contiguous leads: 2.5 mm in men under 40 years, 2 mm in men under 40 years, 1.5 mm in women in leads V<sub>2</sub>–V<sub>3</sub>, and/or 1 mm in the other leads. Increased troponin levels were used for confirmation.<sup>5</sup> Eligible patients experienced symptom onset within 12 hours before hospital admission. Patients were assigned to 2 groups according to AMI onset: Group I included patients with morning onset (between 06:00 and 12:00 hours), and Group II included those with symptom onset at other times of the day.

The time of symptom onset was determined by asking patients to specify the precise time their clinical symptoms began.

### Angiography

Both radial and femoral approaches were employed for coronary angiography and PPCI. Antithrombotic medication was administered to all patients in accordance with current ESC clinical practice guidelines.<sup>6</sup> Ticagrelor (180 mg loading dose) was the preferred P2Y<sub>12</sub> inhibitor unless contraindicated; in such cases, clopidogrel (600 mg loading dose) was used. Unfractionated heparin or low molecular weight heparin was administered, with glycoprotein IIb/IIIa inhibitors used at the operator’s discretion based on the patient’s condition.<sup>6</sup> The thrombolysis in myocardial infarction (TIMI) flow score was assessed before and after PPCI.<sup>7,8</sup>

Off-line interpretation of coronary angiography was performed by 2 experienced interventional cardiologists. Thrombus burden was graded based on the following criteria: G0 (no thrombus), G1 (potential thrombus), G2 (modest, largest dimension 1/2 vascular diameter [VD]), G3 (moderate, >1/2 but 2VD), G4 (large, 2VD), and G5 (unable to estimate thrombus burden due to vessel obstruction). For patients with G5 classification, the thrombus burden score was determined after passing a wire or small, deflated balloon through the lesion.<sup>9</sup>

### Echocardiographic Evaluation

Echocardiographic evaluation was performed using a GE Vivid 7 echocardiography machine with a 2.5 MHz transducer, a commonly available device. Left ventricular ejection fraction was determined using the biplane method of discs.<sup>10</sup>

### Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version

22.0 (IBM Corp, Armonk, NY, USA). All continuous variables passed the Kolmogorov-Smirnov test, a standard test for normality. Data were expressed as mean and standard deviation (SD) for continuous variables and as numbers and frequency percentages for categorical variables. The  $\chi^2$  test was used to compare categorical variables, while an independent-sample *t*-test was employed for normally distributed quantitative data. A *P* value  $\leq 0.05$  was considered statistically significant.

G\*Power software (version 3.1.9.4; Franz Faul, University of Kiel, Germany) was utilized to calculate the power of the sample size. With a 0.05  $\alpha$  level and a medium effect size for different variables, the estimated power value was 0.89.<sup>11</sup>

## RESULTS

This retrospective study enrolled 433 patients with STEMI who underwent PPCI. The patients were divided into 2 groups based on the time of AMI onset: Group I (n=176) consisted of patients with morning AMI onset, while Group II (n=257) included patients with AMI onset during the rest of the day.

### Demographic and Clinical Characteristics (Table 1):

There were no statistically significant differences between the 2 groups concerning age, sex, traditional risk factors, hemodynamic parameters, time delays from symptom onset to wire crossing, baseline serum creatinine, troponin levels, and ejection fraction.

### Angiographic and Procedural Comparison Between the Groups (Table 2):

Patients with morning onset STEMI had a higher thrombus burden, as evidenced by statistically significant higher initial and post-flow achievement thrombus scores ( $P=0.035$  and  $P=0.016$ , respectively) and lower initial TIMI flow scores ( $P=0.004$ ). Additionally, bailout glycoprotein IIb/IIIa usage was significantly higher in Group I ( $P=0.002$ ).

On the other hand, there were no statistically significant differences between the groups in terms of thrombus aspiration rates, final TIMI flow scores, or the length of the implanted stent in the culprit lesion.

**Table 1:** Comparisons of the Demographic and Clinical Characteristics of the 2 Groups

		Group I (N= 176)	Group II (N= 257)	t / $\chi^2$	P value	
Age	Mean $\pm$ SD	58.34 $\pm$ 7.18	58.05 $\pm$ 7.05	0.412	0.681	
Sex	Male	N	123	186	0.316	0.574
		%	69.9%	72.4%		
	Female	N	53	71		
		%	30.1%	27.6%		
Diabetes	No	N	143	206	0.080	0.777
		%	81.3%	80.2%		
	Yes	N	33	51		
		%	18.8%	19.8%		
Hypertension	No	N	128	179	0.480	0.489
		%	72.7%	69.6%		
	Yes	N	48	78		
		%	27.3%	30.4%		
Current smoking	No	N	125	180	0.049	0.826
		%	71.0%	70.0%		
	Yes	N	51	77		
		%	29.0%	30.0%		
Dyslipidemia	No	N	159	227	0.438	0.508
		%	90.3%	88.3%		

Family history	Yes	N	17	30	0.003	0.959
		%	9.7%	11.7%		
	No	N	170	248		
		%	96.6%	96.5%		
Peripheral vascular disease	Yes	N	6	9	0.004	0.952
		%	3.4%	3.5%		
	No	N	168	245		
		%	95.5%	95.3%		
BMI, kg/m <sup>2</sup>	Mean ± SD	29.89 ± 3.48	29.82 ± 3.48	0.182	0.855	
SBP	Mean ± SD	128.85 ± 24.19	127.61 ± 24.63	0.517	0.605	
DBP	Mean ± SD	77.77 ± 11.83	76.82 ± 12.31	0.798	0.425	
HR	Mean ± SD	83.18 ± 16.72	85.05 ± 18.19	1.088	0.277	
Killip class	I	N	152	224	0.524	0.770
		%	86.4%	87.2%		
	II	N	18	22		
		%	10.2%	8.6%		
	III	N	6	11		
		%	3.4%	4.3%		
LVEF, %	Mean ± SD	48.65 ± 6.34	48.72 ± 5.86	0.112	0.911	
Troponin, ng/mL	Mean ± SD	1.43±0.88	1.31±0.69	1.629	0.104	
S creatinine, mg/dL	Mean ± SD	0.94±0.31	0.94±0.33	0.039	0.969	
Hemoglobin, g/dL	Mean ± SD	13.38 ± 1.90	13.42 ± 1.83	0.222	0.824	
Platelets, cell/cmm	Mean ± SD	210.41 ± 37.02	203.84 ± 43.57	1.636	0.103	
TLC, cell/cmm	Mean ± SD	8.18 ± 3.48	7.84 ± 3.19	1.071	0.285	
Time from symptoms onset to STEMI diagnosis	Mean ± SD	172.93 ± 109.58	179.57 ± 126.88	0.565	0.572	
Time from symptoms onset to wire crossing	Mean ± SD	206.39 ± 114.00	212.61 ± 131.38	0.510	0.610	
Time from STEMI diagnosis to wire crossing	Mean ± SD	33.47 ± 12.33	33.04 ± 11.60	0.370	0.711	

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, LVEF: left ventricular ejection fraction, S creatinine: serum creatinine, TLC: total leukocyte count, STEMI: ST-segment elevation myocardial infarction

**Table 2:** Comparisons of the Angiographic Characteristics of the 2 Groups

		Group I (N= 176)	Group II (N= 257)	t / $\chi^2$	P value	
IRA	LAD	N	96	144	0.972	0.965
		%	54.5%	56.0%		
	LCX	N	25	33		
		%	14.2%	12.8%		
	RCA	N	48	70		
		%	27.3%	27.2%		
	Venus graft	N	2	5		
		%	1.1%	1.9%		
Ramus	N	2	2			
	%	1.1%	0.8%			
Diagonal	N	3	3			
	%	1.7%	1.2%			
Initial thrombus burden score	Grade I	N	4	10	10.323	0.035*
		%	2.3%	3.9%		
	Grade II	N	4	12		
		%	2.3%	4.7%		
	Grade III	N	6	16		
		%	3.4%	6.2%		
	Grade IV	N	15	39		
		%	8.5%	15.2%		

	Grade V	%	8.5%	15.2%	13.941	0.016*
		N	147	180		
		%	83.5%	70.0%		
Thrombus burden post flow achievement	Grade 0	N	8	15	13.362	0.004*
		%	4.5%	5.8%		
	Grade I	N	17	41		
		%	9.7%	16.0%		
	Grade II	N	8	30		
		%	4.5%	11.7%		
	Grade III	N	49	66		
		%	27.8%	25.7%		
	Grade IV	N	100	101		
%		51.2%	39.3%			
Grade V (failure to achieve flow)	N	4	4			
	%	2.3%	1.6%			
Initial TIMI flow score	Grade 0	N	139	165	3.205	0.361
		%	79.0%	64.2%		
	Grade I	N	26	52		
		%	14.8%	20.2%		
	Grade II	N	10	31		
		%	5.7%	12.1%		
Grade III	N	1	9			
	%	0.6%	3.5%			
Final TIMI flow score	Grade 0	N	4	4	10.061	0.002*
		%	2.3%	1.6%		
	Grade I	N	8	9		
		%	4.5%	3.5%		
	Grade II	N	19	17		
		%	10.8%	6.6%		
Grade III	N	145	227			
	%	82.4%	88.3%			
Glycoprotein IIb/ IIIa	No	N	138	230	0.011	0.917
		%	78.4%	89.5%		
	Yes	N	38	27		
		%	21.6%	10.5%		
Use of thrombus aspiration	No	N	166	243	0.162	0.872
		%	94.3%	94.6%		
	Yes	N	10	14		
		%	5.7%	5.4%		
Stent diameter	Mean ± SD	3.11 ± 0.32	3.12 ± 0.31	0.162	0.872	
Stent length	Mean ± SD	25.11 ± 8.58	25.51 ± 8.34	0.491	0.623	

IRA: infarct-related artery, LAD: left anterior descending, LCX: left circumflex, RCA, right coronary artery, TIMI: thrombolysis in myocardial infarction

## DISCUSSION

Circadian rhythm plays a significant role in regulating human physiological behavior. Disturbances in circadian rhythm have been associated with various cardiovascular events such as MI, stroke, and adverse cardiac events, as well as obesity, sleep disorders, metabolic disorders, and psychiatric illnesses. The circadian cycle influences a broad spectrum of physiological and metabolic processes.<sup>12</sup>

Every system in our body operates on a 24-hour rhythm each day. This circadian rhythm also governs the heart and vasculature, affecting various cardiovascular processes such as platelet aggregability, vascular tone, and the response to oxidative stress. These changes could explain the observed relative increase in cardiovascular events during the early morning hours.<sup>13</sup>

Although numerous studies have explored the influence of circadian rhythm on MI,

angiographic findings in patients presenting during morning hours have not been extensively investigated.

Our study's primary findings indicate that patients experiencing AMI onset between 06:00 and 12:00 exhibited a higher thrombus burden, lower patency in the infarct-related artery during coronary angiography, and a slightly increased incidence of no-reflow. Additionally, the use of bailout glycoprotein IIb/IIIa and thrombus aspiration in the catheterization laboratory was marginally higher in this group.

Several studies, including one by Fang Zhao et al,<sup>14</sup> have demonstrated a higher incidence of MI during the morning hours, particularly in individuals with obstructive sleep apnea. These findings chime with those of other investigations that have reported an increased incidence of MI in the morning.

The development of unstable atherosclerotic lesions is considered a critical step in the onset of ACS. Various inflammatory processes play a significant role in determining plaque vulnerability, with immune system activation within the plaque and thrombogenic factors in the circulating blood contributing to this instability.<sup>15,16</sup>

Moreover, transient biological and physiological changes related to the circadian rhythm that occur in the early morning may play a substantial role in the development of ACS.<sup>17</sup>

In addition to increased sympathetic tone, the rise in blood pressure, platelet activation, coagulability, and impaired fibrinolysis balance during the early morning hours may contribute to a prothrombotic environment. These factors may potentially lead to plaque instability and rupture.<sup>18</sup>

The early morning increase in blood pressure and heart rate elevates myocardial oxygen demand while reducing coronary blood flow.<sup>19</sup>

Circadian rhythm may influence the quantity and activity of circulating platelets,

potentially involving catecholamines in this process.<sup>20</sup>

Circadian rhythm has been associated with the activation of clotting factors, such as Factor VII, fibrinogen, and prothrombin, as well as the morning decrease in the activity of fibrinolytic system components like plasminogen activator inhibitor-1 and tissue plasminogen activator.<sup>21</sup>

The intricate interplay between the 2 primary processes—cardiac oxygen demand/supply and coagulation/fibrinolytic systems—and their variations may contribute to the onset of ACS in the morning.<sup>22</sup>

The significant associations between neurohormonal fluctuations, prothrombotic conditions, and hemodynamic effects, which are implicated in the pathogenesis of myocardial infarction in the morning, may explain our findings.

## CONCLUSIONS

Patients with AMI presenting during the morning hours (06:00 to 12:00) exhibited a higher thrombus burden, increased incidence of total occlusion of the infarct-related artery, and no-reflow. In these cases, there was a greater tendency to utilize bailout glycoprotein IIb/IIIa inhibitors during PPCI. Further multicenter studies are recommended to validate our findings and investigate whether these observations should influence the management approach for STEMI patients presenting in the early morning hours. Potential management strategies may include the upstream use of glycoprotein IIb/IIIa inhibitors before PPCI, intracoronary administration of glycoprotein IIb/IIIa inhibitors, vasodilators to improve coronary microcirculation (eg, nitroprusside, adenosine, and calcium channel blockers), manual thrombus aspiration, embolic protection devices, and direct or deferred stenting.

**Disclosure:**

**Ethics Approval and Consent to Participate:** All the patients provided written informed consent, and the study was approved by the Ethics Committee of the Tanta University Faculty of Medicine. All methods were carried out per relevant guidelines and regulations (committee reference number: 36217/12/22).

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